

## Behavioural pharmacology

Morphine modulates the effects of histamine H<sub>1</sub> and H<sub>3</sub> receptors on seizure susceptibility in pentylenetetrazole-induced seizure model of mice

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## ABSTRACT

Histamine regulates release of neurotransmitters such as dopamine, serotonin, gamma-aminobutyric acid (GABA), glutamate and also is involved in several functions in central nervous system (CNS). It has been shown that histamine participates in disorders like seizure. It has been well documented that morphine dose-dependently induces anti or proconvulsant effects. In the current study, we firstly showed that morphine (1 mg/kg) exerts anticonvulsant effects which significantly reversed by naltrexone administration. Secondly, we determined seizure threshold for H<sub>1</sub> and H<sub>3</sub> receptors agonists and antagonists in mouse model of pentylenetetrazole (PTZ)-induced clonic seizures. Our results showed that activation of H<sub>1</sub> receptors by 2-(2-Pyridyl)-ethylamine exerts anticonvulsant properties while inhibition of H<sub>1</sub> receptors by pyrilamine maleate induced proconvulsant effects. Furthermore, we showed that imipenem dihydrobromide, a H<sub>3</sub> receptor agonist, increased seizure susceptibility to PTZ whereas thio-peramide, a H<sub>3</sub> receptor antagonist increased seizure threshold. We also revealed that pretreatment with morphine potentially reversed the effects of histaminergic system on seizure threshold suggesting the involvement of opioid system in alteration of seizure threshold by histaminergic drugs.

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## 1. Introduction

Histamine [2-(4-imidazolyl)-ethylamine], an endogenous biogenic amine, mediates pleiotropic functions in the central nervous system (CNS) (Fernandez-Novoa and Cacabelos, 2001). Histaminergic neurons are located in tuberomammillary nucleus of hypothalamus and projects to practically all major brain regions (Haas and Panula, 2003). This neurotransmitter has been implicated in regulation of several CNS activities such as cognition, arousal, circadian rhythms, synaptic plasticity, pain perception, stress, anxiety, and neuroendocrine regulation (Brown et al.,

2001). Evidence indicates histamine modulates the release of other neurotransmitters such as dopamine, serotonin, nor-epinephrine and gamma-aminobutyric acid (GABA) (Flik et al., 2015). Since histamine participates in variety of brain pathologies, it has been suggested that histaminergic system would be an appropriate therapeutic target for treatment of neuropathic pain, sleep-wake disorders, attention deficit hyperactivity disorder, Alzheimer's disease, Parkinson's disease, schizophrenia, migraine and epilepsy (Alstadhaug, 2014; Gemkow et al., 2009; Passani and Blandina, 2011).

Clinical and preclinical studies have suggested the possible involvement of histaminergic system in seizure disorders (Stark, 2003). In this regard, previous research demonstrated that increased level of central histamine acts as an endogenous anticonvulsant agent and exerts an important inhibitory effect during seizure episodes (Bhowmik et al., 2012). Using animal models of electrically/chemically-induced seizure, it has been shown that activation of the histaminergic system, mainly through H<sub>1</sub>

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receptor, increase seizure threshold in animals (Hirai et al., 2004; Tuomisto and Tacke, 1986). However, applying  $H_1$  receptor antagonists exhibited proconvulsant effects in animal studies (Cermínara et al., 2013). Moreover, there are pieces of evidence indicating the involvement of  $H_3$  receptors in the seizure activity (Harada et al., 2004; Sadek et al., 2014). A number of investigations have revealed that  $H_3$  receptor antagonists not only mitigate the severity of epileptic symptoms but protect neurons against seizure-associated neurotoxicity through enhancing the release of histamine, GABA and also, histidine decarboxylase activity (Bhowmik et al., 2012; Devi et al., 2011).

On the other hand, evidence suggests that opioids exert both proconvulsant and anticonvulsant effects in different animal models of seizure (Homayoun et al., 2002b; Lauretti et al., 1994). While low doses of morphine have been reported to reduce the seizure susceptibility to picrotoxin, bicuculline and pentylenetetrazol (PTZ), higher doses induce proconvulsant effects that indicating the biphasic effects of morphine on seizure threshold (Frenk, 1983; Lauretti et al., 1994). Considering that opioid receptors possess seizure-modulating properties, they may have functional interactions with other receptor classes involved in seizure activity (Shafaroodi et al., 2004). Considering that both opioid and histamine receptors share physiological properties such as anti-nociception, a possible interaction may exist between these two classes of receptors in controlling seizures. The purpose of the current study is to examine whether opioid system may play a role in mediating the effects of histamine  $H_1$  and  $H_3$  receptor agonists/antagonists on seizure susceptibility to PTZ.

## 2. Materials and methods

### 2.1. Animals

Male NMRI mice weighing  $27 \pm 3$  g (Pasteur Institute, Tehran, Iran) were used in this study. Animals were housed in standard polycarbonate cages (4–5 mice per cage) and under standard laboratory conditions (12-h light/dark cycle, temperature  $(22 \pm 1^\circ\text{C})$  and free access to food and water). All behavioral experiments were performed between 10:00 a.m. and 13:00 p.m. All procedures in this study were carried out in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (NIH Publication no. 80-23) and institutional guidelines for animal care and use (Department of Pharmacology, School of Medicine, TUMS). Each mouse underwent treatment only once and also each treatment group was consisted of 8 animals.

### 2.2. Drugs

The drugs used in this study were as follows: morphine sulfate, pentylenetetrazole (Sigma, U.K.), naltrexone, 2-(2-Pyridyl)-ethylamine, pyrilamine maleate, immepip dihydrobromide and thioperamide maleate (Sigma, St Louis, MO, USA). All drugs were dissolved in 0.9% saline in a volume of 10 ml/kg. In order to assess clonic seizures in experimental animals, PTZ was administered intravenously (0.5%, i.v.) and all other drugs were administered intraperitoneally (i.p.). Doses of each drug were selected based on our previous and pilot studies (Honar et al., 2004).

### 2.3. Treatment

Experiment 1 examined the effect of morphine (1 mg/kg) on clonic seizure threshold. Animals in this experiment received morphine 30 min before PTZ administration.

In experiment 2 we examined the effect of naltrexone (10 mg/

kg) along with morphine (1 mg/kg) on clonic seizure threshold. Animals in this trial received naltrexone 15 min prior to morphine injection and 45 min before the administration of PTZ.

Experiment 3 examined the effect of 2-(2-Pyridyl)-ethylamine ( $H_1$  agonist, 5 mg/kg) alone (30 min before the test) or along with morphine (1 mg/kg, 15 min prior to 2-(2-Pyridyl)-ethylamine) on seizure threshold.

In experiment 4 effect of pyrilamine maleate ( $H_1$  antagonist, 10 mg/kg) alone (30 min before the test) or along with morphine (1 mg/kg, 15 min before pyrilamine maleate) on seizure threshold was determined.

Experiment 5 was designed to examine the effect of immepip dihydrobromide ( $H_3$  agonist, 10 mg/kg) alone (30 min before the test) or in combination with morphine (1 mg/kg, 15 min prior to immepip dihydrobromide) on seizure threshold.

Experiment 6 examined the effect of thioperamide ( $H_3$  antagonist, 10 mg/kg) alone (30 min before the test) or along with morphine (1 mg/kg, 15 min before thioperamide maleate) on seizure threshold.

### 2.4. Determination of seizure threshold

We assessed the seizure threshold using the method that was previously described in our previous studies (Amiri et al., 2014; Amini-Khoei et al., 2015). To determine the clonic seizure threshold, we inserted a 30-gauge butterfly needle into the lateral tail vein of mice. The needle was then fixed to the tail by a piece of adhesive tape. With the mouse moving freely, the PTZ solution (0.5%) was slowly infused into the tail vein at a constant rate of 1 ml/min, using an infusion pump (NE 1000, New Era Pump System, Inc.), which was connected to the dental needle by polyethylene tubing. Infusion was halted when forelimb clonus followed by full clonus of the body (began with running and then loss of righting ability) was observed. The minimal dose of PTZ (mg/kg of mice weight) needed to induce general clonus was recorded as an index of clonic seizure threshold. In this regard, the seizure threshold is dependent on PTZ dose administered and time-related.

### 2.5. Statistics

The one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test was used to analyze the data. Values are expressed as mean  $\pm$  S.E.M., a value of  $P < 0.05$  was considered as statistically significant in all experiments.

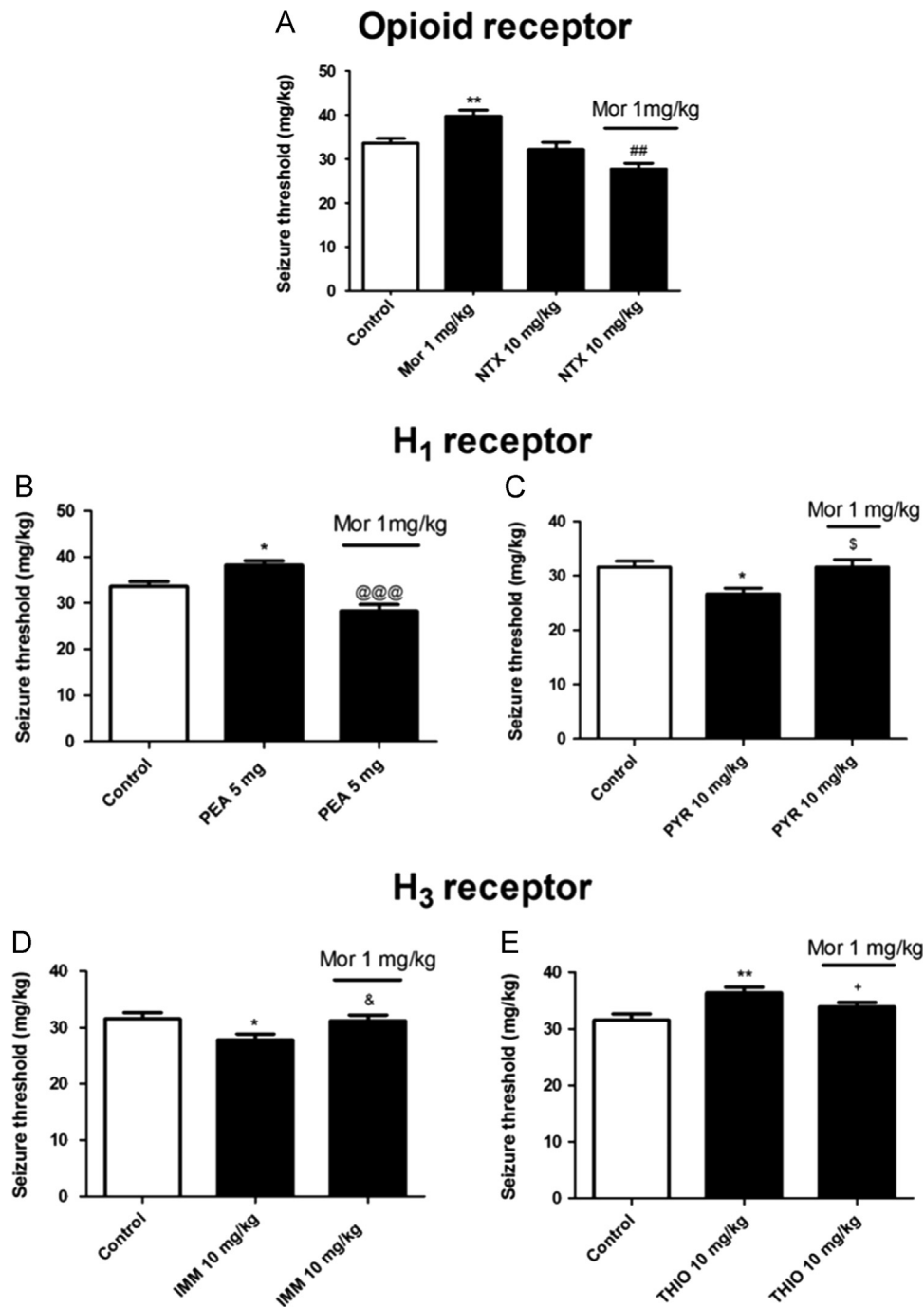
## 3. Results

### 3.1. Effects of morphine and naltrexone on seizure threshold

As shown in Fig. 1A, administration of morphine (30 min before the test) significantly increased seizure threshold in animals ( $**P < 0.01$ ). In addition, pretreatment with naltrexone (15 min prior to morphine treatment) significantly decreased seizure threshold ( $***P < 0.01$ ). Furthermore, naltrexone by its own had no effect on seizure threshold ( $P > 0.05$ ).

### 3.2. Effect of 2-(2-Pyridyl)-ethylamine ( $H_1$ agonist) on the PTZ-induced seizures

Fig. 1B shows the effect of morphine pretreatment on the anticonvulsant effect of 2-(2-Pyridyl)-ethylamine against PTZ-induced seizures. Administration of 2-(2-Pyridyl)-ethylamine significantly increased the seizure threshold in comparison with saline-treated controls ( $*P < 0.05$ ). Moreover, morphine



**Fig. 1.** Effects of different treatments on seizure threshold in PTZ model of clonic seizures in mice: (A) Effects of morphine (Mor) and naltrexone (NTX) treatments on seizure threshold. (B) Effects of 2-(2-Pyridyl)-ethylamine (PEA) and morphine on seizure threshold. (C) Effects of pyrilamine maleate (PYR) and morphine on seizure threshold. (D) Effects of immepip dihydrobromide (IMM) and morphine on seizure threshold. (E) Effects of thioperamide maleate (THIO) and morphine on seizure threshold. Data are expressed as mean  $\pm$  S.E.M. ( $n=8$ ) and were analyzed by one-way ANOVA and Tukey's post-hoc test. \* $P < 0.05$  and \*\* $P < 0.01$  compared with saline-treated controls in each figure. \*\*\* $P < 0.001$  compared with morphine treated group in Fig. 1A. @@@ $P < 0.001$  compared with PEA treated group in Fig. 1B. \$ $P < 0.05$  compared with PYR treated group in Fig. 1C. & $P < 0.05$  compared with IMM treated group in Fig. 1D. + $P < 0.05$  compared with THIO treated group in Fig. 1E.

pretreatment decreased the anticonvulsant effect of 2-(2-Pyridyl)-ethylamine (@@@ $P < 0.001$ ).

### 3.3. Effect of pyrilamine maleate ( $H_1$ antagonist) on the PTZ-induced seizures

Fig. 1C shows the effect of morphine pretreatment on the proconvulsant effect of pyrilamine maleate against PTZ-induced seizures. Administration of pyrilamine maleate significantly decreased the seizure threshold in comparison with saline-treated

controls (\* $P < 0.05$ ). As shown in Fig. 1C, morphine pretreatment significantly reversed the proconvulsant effect of pyrilamine maleate (\$ $P < 0.05$ ).

### 3.4. Effect of immepip dihydrobromide ( $H_3$ agonist) on the PTZ-induced seizures

As shown in Fig. 1D, administration of immepip dihydrobromide significantly decreased the seizure threshold in comparison with saline-treated controls (\* $P < 0.05$ ). Furthermore,

morphine pretreatment led to an increase in seizure threshold when compared with IMM treated group ( $^*P < 0.05$ ).

### 3.5. Effect of thioperamide maleate ( $H_3$ antagonist) on the PTZ-induced seizures

As shown in Fig. 1E, administration of thioperamide maleate significantly increased the seizure threshold in comparison with saline-treated controls ( $^{**}P < 0.01$ ). Also, morphine pretreatment reversed the anticonvulsant effect of thioperamide maleate ( $^+P < 0.05$ ).

## 4. Discussion

Results of the present study revealed that  $H_1$  and  $H_3$  receptors play a role in seizure susceptibility to PTZ and also, opioid system is involved in their effects. In contrast to  $H_3$  receptors, activation of  $H_1$  receptors by its agonists produced anticonvulsant effect and application of  $H_1$  antagonists led to a decrease in seizure threshold. In addition, modulatory effects of morphine on histaminergic-induced alterations in seizure threshold suggest the interaction between opioid and histaminergic system in seizure susceptibility to PTZ.

While vast majority of investigations in epilepsy have focused on inhibitory and excitatory neurotransmissions, role of other contributing neurotransmitters, such as histamine and its interactions with other neurotransmission systems have not been studied well. Evidence indicates that histaminergic system has many interactions with excitatory and inhibitory neurotransmission. Once couples to GABAergic and glutamatergic systems, histamine is able to regulate histaminergic activity through interactions with GABA<sub>A</sub>, GABA<sub>B</sub> and NMDA receptors. Moreover, histamine inhibits the release of several neurotransmitters, such as GABA, glutamate, dopamine, serotonin, noradrenaline and acetylcholine via  $H_3$  receptors (Brown et al., 2001; Lintunen et al., 2005). There are pieces of evidence suggesting that unlike  $H_1$  receptor antagonists, activation of the central histaminergic system by  $H_1$  receptor agonists positively modifies seizure activity (Kukko-Lukjanov et al., 2012; Miyata et al., 2011).

Our results were consistent with these studies that administration of 2-(2-Pyridyl)-ethylamine led to an increase in seizure susceptibility to PTZ while pyrilamine maleate produced proconvulsant effect. Considering that  $H_3$  receptors are inhibitory auto-receptors in histaminergic neurons, previous studies have shown that  $H_3$  receptor antagonists are able to mitigate seizure susceptibility by increasing the release of histamine in brain (Bhowmik et al., 2012; Trenité et al., 2013). In this context, thioperamide, a selective  $H_3$  receptor antagonist, has been reported to decrease seizure vulnerability to PTZ via increasing the endogenous histamine levels in brain (Vohora et al., 2000). In agreement with previous investigations, our results corroborated the anticonvulsant properties of  $H_3$  receptor antagonists that mice treated with immepip dihydrobromide exhibited more sensitivity to convulsing effects of PTZ while treating animals with thioperamide induced an anticonvulsant effect. In this context, it has been reported that  $H_3$ -receptor agonists or  $H_1$ -receptor antagonists increase seizure susceptibility in different models of seizures including amygdaloid kindling, maximal electroshock, picrotoxin and pentylenetetrazol-induced seizures (Sturman et al., 1994; Vohora et al., 2001).

On the other hand, components of opioid system have been widely distributed in CNS and play an important role in regulation of many behavioral and cognitive processes such as pain, neurotransmission and seizure activity (Akil et al., 1984; Khan et al., 2015). Using different experimental models of seizures, it has been

shown that opioids dose-dependently exert anticonvulsant and proconvulsant effects (Gooshe et al., 2015; Homayoun et al., 2002b). Surprisingly, in contrast to higher doses of morphine, lower doses of morphine have anticonvulsant properties (Homayoun et al., 2002a). Morphine in high doses induces excitation and causes myoclonus seizures (Gregory et al., 1992; Hagen and Swanson, 1997). Previous studies suggest that proconvulsant effect of morphine may be associated with production of 3-glucuronide (a morphine metabolite) (Hemstapat et al., 2003), or nitric oxide (Khavandgar et al., 2002). Further investigations have also suggested that multiple receptor systems such as adrenergic and glutamatergic receptors (Homayoun et al., 2002a; Schroeder et al., 1998) or inhibition of GABAergic neurotransmission (Werz and MacDonald, 1982) are involved in triggering opioid-induced seizures.

Focusing on histaminergic system, past studies demonstrated that histaminergic system mediates some of the central effects of morphine and acute treatment with morphine enhances the turnover of neuronal histamine (Karadag et al., 2000). A study by Karadag et al. (1996) has recently showed that  $H_1$ -receptor antagonists and naloxone are able to antagonize the anticonvulsant effect of morphine. Moreover, it has been reported that phospholipase C and calcium-linked transduction systems are related to opioid receptor activation which consequently lead to degranulation of mast cell and histamine release (Rehni et al., 2010). Results of the current work showed that Co-administration of morphine with both  $H_1$  and  $H_3$  agonists/antagonists reversed their effects on seizure susceptibility to PTZ indicating the interaction between opioid system and histaminergic system in mediating the seizure activity. Also, these data suggests the involvement of opioid system in different effects of histaminergic system on seizure susceptibility to PTZ as a GABA<sub>A</sub> antagonist (Di Capite and Parekh, 2009; Liu and Gintzler, 2006; Lü et al., 2013). Furthermore, it has been reported that opioid receptor-induced seizures is correlated with a significant increase in histamine release that may mediate the proconvulsant properties of morphine (Zhu-Ge et al., 2007). In this regard, Rehni et al. demonstrated that proconvulsant effect of amisulpride may be associated with opioid system-induced activation of histamine receptors. They also showed that pretreatment with a  $H_1$  blocker or a mast cell stabilizer significantly attenuated the amisulpride-induced seizures in mice (Rehni et al., 2011).

## 5. Conclusion

In conclusion, results of our study showed that pretreatment with morphine potentially reversed the effects of histaminergic system ( $H_1$  and  $H_3$ ) on seizure susceptibility to PTZ in mice. Also, our results suggest that opioid system is partially involved in the effects of histamine on seizure activity.

## References

- Akil, H., Watson, S.J., Young, E., Lewis, M.E., Khachaturian, H., Walker, J.M., 1984. Endogenous opioids: biology and function. *Annu. Rev. Neurosci.* 7, 223–255.
- Alstadhaug, K.B., 2014. Histamine in migraine and brain. *Headache* 54, 246–259.
- Amini-Khoei, H., Amiri, S., Shirzadian, A., Haj-Mirzaian, A., Aljanpour, S., Rahimi-Balaei, M., Mohammadi-Asl, A., Hassanipour, M., Mehr, S.E., Dehpour, A.R., 2015. Experiencing neonatal maternal separation increased the seizure threshold in adult male mice: involvement of the opioid system. *Epilepsy Behav.* 52, 37–41.
- Amiri, S., Shirzadian, A., Haj-Mirzaian, A., Imran-Khan, M., Balaei, M.R., Kordjazy, N., Dehpour, A.R., Mehr, S.E., 2014. Involvement of the nitric system in the proconvulsant effect of social isolation stress in male mice. *Epilepsy Behav.* 41, 158–163.
- Bhowmik, M., Khanam, R., Vohora, D., 2012. Histamine  $H_3$  receptor antagonists in relation to epilepsy and neurodegeneration: a systemic consideration of recent



- progress and perspectives. *Br. J. Pharmacol.* 167, 1398–1414.
- Brown, R.E., Stevens, D.R., Haas, H.L., 2001. The physiology of brain histamine. *Prog. Neurobiol.* 63, 637–672.
- Cerminara, C., El-Malhany, N., Roberto, D., Lo, C.A., Curatolo, P., 2013. Seizures induced by desloratadine, a second-generation antihistamine: clinical observations. *Neuropediatrics* 44, 222–224.
- Devi, P.U., Manocha, A., Khanam, R., Vohora, D., 2011. Beneficial interaction between clobenpropit and pyridoxine in prevention of electroshock induced seizures in mice: lack of histaminergic mechanisms. *Hum. Exp. Toxicol.* 30 (1), 84–88.
- Di Capite, J., Parekh, A.B., 2009. CRAC channels and  $Ca^{2+}$  signaling in mast cells. *Immunol. Rev.* 231, 45–58.
- Fernandez-Novoa, L., Cacabelos, R., 2001. Histamine function in brain disorders. *Behav. Brain Res.* 124, 213–233.
- Flik, G., Folgering, J.H., Cremers, T.I., Westerink, B.H., Dremencov, E., 2015. Interaction between brain histamine and serotonin, norepinephrine, and dopamine systems: in vivo microdialysis and electrophysiology study. *J. Mol. Neurosci.* 56, 1–9.
- Frenk, H., 1983. Pro- and anticonvulsant actions of morphine and the endogenous opioids: involvement and interactions of multiple opiate and non-opiate systems. *Brain Res. Rev.* 6, 197–210.
- Gemkow, M.J., Davenport, A.J., Harich, S., Ellenbroek, B.A., Cesura, A., Hallett, D., 2009. The histamine H3 receptor as a therapeutic drug target for CNS disorders. *Drug. Discov. Today* 14, 509–515.
- Gooshe, M., Abdolghaffari, A.H., Aleyasin, A.R., Chabouk, L., Tofigh, S., Hassanzadeh, G.R., Payandemehr, B., Partoazar, A., Azizi, Y., Dehpour, A.R., 2015. Hypoxia/ischemia a key player in early post stroke seizures: modulation by opioidergic and nitrenergic systems. *Eur. J. Pharmacol.* 746, 6–13.
- Gregory, R.E., Grossman, S., Sheidler, V.R., 1992. Grand mal seizures associated with high-dose intravenous morphine infusions: incidence and possible etiology. *Pain* 51, 255–258.
- Haas, H., Panula, P., 2003. The role of histamine and the tuberomammillary nucleus in the nervous system. *Nat. Rev. Neurosci.* 4, 121–130.
- Hagen, N., Swanson, R., 1997. Strychnine-like multifocal myoclonus and seizures in extremely high-dose opioid administration: treatment strategies. *J. Pain. Symptom Manag.* 14, 51–58.
- Harada, C., Hirai, T., Fujii, Y., Harusawa, S., Kurihara, T., Kamei, C., 2004. Intracerebroventricular administration of histamine H3 receptor antagonists decreases seizures in rat models of epilepsy. *Methods Find. Exp. Clin. Pharmacol.* 26, 263–270.
- Hemstapat, K., Monteith, G.R., Smith, D., Smith, M.T., 2003. Morphine-3-glucuronide's neuro-excitatory effects are mediated via indirect activation of N-methyl-D-aspartic acid receptors: mechanistic studies in embryonic cultured hippocampal neurones. *Anesth. Analg.* 97, 494–505.
- Hirai, T., Okuma, C., Harada, C., Mio, M., Ohtsu, H., Watanabe, T., Kamei, C., 2004. Development of amygdaloid kindling in histidine decarboxylase-deficient and histamine H1 receptor-deficient mice. *Epilepsia* 45, 309–313.
- Homayoun, H., Khavandgar, S., Dehpour, A.R., 2002a. The role of  $\alpha_2$ -adrenoceptors in the modulatory effects of morphine on seizure susceptibility in mice. *Epilepsia* 43, 797–804.
- Homayoun, H., Khavandgar, S., Namiranian, K., Gaskari, S.A., Dehpour, A.R., 2002b. The role of nitric oxide in anticonvulsant and proconvulsant effects of morphine in mice. *Epilepsy Res.* 48, 33–41.
- Honar, H., Riaz, K., Homayoun, H., Sadeghipour, H., Rashidi, N., Ebrahimkhani, M., Mirazi, N., Dehpour, A., 2004. Ultra-low dose naltrexone potentiates the anticonvulsant effect of low dose morphine on clonic seizures. *Neuroscience* 129, 733–742.
- Karadag, Ç.H., Ulugöl, A., Dökmeci, D., Dökmeci, I., 1996. The role of histamine H1-receptors in the anticonvulsive effect of morphine against maximal electroconvulsive shock in mice. *Jpn. J. Pharmacol.* 71, 109–112.
- Karadag, C., Dokmeci, D., Dost, T., Ulugöl, A., Dokmeci, I., 2000. Compound 48/80, a histamine-depleting agent, blocks the protective effect of morphine against electroconvulsive shock in mice. *Braz. J. Med. Biol. Res.* 33, 327–330.
- Khan, M.I., Shirzadian, A., Haj-Mirzaian, A., Mehr, S.E., Dehpour, A.R., Rahimi-Balaei, M., Amiri, S., 2015. Proconvulsant effect of post-weaning social isolation stress may be associated with dysregulation of opioid system in the male mice. *Med. Hypotheses* 84, 445–447.
- Khavandgar, S., Homayoun, H., Dehpour, A.R., 2002. The role of nitric oxide in the proconvulsant effect of  $\delta$ -opioid agonist SNC80 in mice. *Neurosci. Lett.* 329, 237–239.
- Kukko-Lukjanov, T.-K., Grönman, M., Lintunen, M., Laurén, H.B., Michelsen, K.A., Panula, P., Holopainen, I.E., 2012. Histamine 1 receptor knock out mice show age-dependent susceptibility to status epilepticus and consequent neuronal damage. *Epilepsy Res.* 100, 80–92.
- LÜ, F., Lin, J., Benditt, D.G., 2013. Conscious sedation and anesthesia in the cardiac electrophysiology laboratory. *J. Cardiovasc. Electrophysiol.* 24, 237–245.
- Lauretti, G.R., Ahmad, I., Pleuvry, B., 1994. The activity of opioid analgesics in seizure models utilizing N-methyl-DL-aspartic acid, kainic acid, bicuculline and pentylentetrazole. *Neuropharmacology* 33, 155–160.
- Lintunen, M., Sallmen, T., Karlstedt, K., Panula, P., 2005. Transient changes in the limbic histaminergic system after systemic kainic acid-induced seizures. *Neurobiol. Dis.* 20, 155–169.
- Liu, N.-J., Gintzler, A.R., 2006. Phospholipase C $\beta$ 1 modulates pain sensitivity, opioid antinociception and opioid tolerance formation. *Brain Res.* 1069, 47–53.
- Miyata, I., Saegusa, H., Sakurai, M., 2011. Seizure-modifying potential of histamine H1 antagonists: a clinical observation. *Pediatr. Int.* 53, 706–708.
- Passani, M.B., Blandina, P., 2011. Histamine receptors in the CNS as targets for therapeutic intervention. *Trends Pharmacol. Sci.* 32, 242–249.
- Rehni, A.K., Singh, T.G., Chand, P., 2011. Amisulpride-induced seizurogenic effect: a potential role of opioid receptor-linked transduction systems. *Basic Clin. Pharmacol. Toxicol.* 108, 310–317.
- Rehni, A.K., Singh, T.G., Singh, N., Arora, S., 2010. Tramadol-induced seizurogenic effect: a possible role of opioid-dependent histamine (H1) receptor activation-linked mechanism. *Naunyn Schmiedeberg's Arch. Pharmacol.* 381, 11–19.
- Sadek, B., Kuder, K., Subramanian, D., Shafullah, M., Stark, H., Lazewska, D., Adem, A., Kiec-Kononowicz, K., 2014. Anticonvulsive effect of nonimidazole histamine H3 receptor antagonists. *Behav. Pharmacol.* 25, 245–252.
- Schroeder, H., Becker, A., Grecksch, G., Schroeder, U., Hoell, V., 1998. The effect of pentylentetrazol kindling on synaptic mechanisms of interacting glutamatergic and opioid system in the hippocampus of rats. *Brain Res.* 811, 40–46.
- Shafaroodi, H., Samini, M., Moezi, L., Homayoun, H., Sadeghipour, H., Tavakoli, S., Hajrasouliha, A.R., Dehpour, A.R., 2004. The interaction of cannabinoids and opioids on pentylentetrazole-induced seizure threshold in mice. *Neuropharmacology* 47, 390–400.
- Stark, H., 2003. Recent advances in histamine H3/H4 receptor ligands. *Expert. Opin. Ther. Pat.* 13, 851–865.
- Sturman, G., Freeman, P., Meade, H., Seeley, N., 1994. Modulation of the intracellular and H3-histamine receptors and chemically-induced seizures in mice. *Agents Actions* 41, C68–C69.
- Trenité, D.K.-N., Parain, D., Genton, P., Masnou, P., Schwartz, J.-C., Hirsch, E., 2013. Efficacy of the histamine 3 receptor (H3R) antagonist pitolisant (formerly known as tipolisant; BF2. 649) in epilepsy: dose-dependent effects in the human photosensitivity model. *Epilepsy Behav.* 28, 66–70.
- Tuomisto, L., Tacke, U., 1986. Is histamine an anticonvulsive inhibitory transmitter? *Neuropharmacology* 25, 955–958.
- Vohora, D., Pal, S., Pillai, K., 2000. Thioperamide, a selective histamine H3 receptor antagonist, protects against PTZ-induced seizures in mice. *Life Sci.* 66, PL297–PL301.
- Vohora, D., Pal, S., Pillai, K., 2001. Histamine and selective H3-receptor ligands: a possible role in the mechanism and management of epilepsy. *Pharmacol. Biochem. Behav.* 68, 735–741.
- Werz, M.A., MacDonald, R.L., 1982. Opiate alkaloids antagonize postsynaptic glycine and GABA responses: correlation with convulsant action. *Brain Res.* 236, 107–119.
- Zhu-Ge, Z., Zhu, Y., Wu, D., Jin, C., Chen, Z., 2007. Involvement of endogenous histamine in modulatory effect of morphine on seizure susceptibility in mice. *J. Zhejiang Univ. Sci.* 36 (130–133), 154.